to CD40 ligand are indefinite. The Examiner admits that there is direction and guidance to the CD40 - specific antibodies and CD40 ligand. However, the Examiner asserts that the defining structural features of the adjuvants are either unknown or ill-defined and ambiguous. More particularly the Examiner asserts that the Specification discloses that the claimed adjuvant includes references to any string of amino acids or ligand which is selected so as to bind to at least part of CD40 but asserts that it is unclear what the scope is of the "string of amino acids".

The Examiner further asserts that it is not sufficient to simply bind to at least a part of CD40 to provide for adjuvant properties, since the Examiner asserts there are both agonistic and antagonistic CD40 - specific antibodies. The Examiner asserts that agonistic antibodies need to be cross-linked in some manner to provide augmentation of the immune response and lymphocyte signaling. The Examiner further asserts that parts of the CD40 ligand would not necessarily result in sufficient signaling associated with the claimed adjuvants and that it would be expected that parts of the CD40 ligand or targeting parts of CD40 would also serve to antagonize the activity of lymphocyte responses. The Examiner finally asserts that adjuvants with CD40 ligand or antibodies that bind CD40, but do not have the appropriate conformation or sufficient multivalency to stimulate lymphocyte responses associated with the claimed properties of the adjuvant have not been enabled.

The Applicant respectfully traverses the Examiner's rejections. The Applicant has amended the Claims to particularly point out and distinctly claim that which he regards as his invention. The amendments have also removed the terms that the Examiner has objected to. Furthermore, the Examiner has determined that the present Specification provides both direction and guidance to CD40-specific antibodies and CD40 ligand, and in addition has withdrawn the rejections regarding "parts thereof" in regard to CD40-specific antibodies. Therefore, the invention is distinctly claimed, and amply described and fully enabled by the instant Specification.

The Applicant traverses the Examiner's assertion that there are both agonistic and antagonistic CD40 -specific antibodies by respectfully pointing out that all characterized anti-CD40 antibodies have been classified into two separate groups: (i) agonists that can induce B-cell proliferation on their own and (ii) non-agonists which cannot induce B-cell proliferation in the absence of another agent. To the Applicant's knowledge no anti-CD40 antibodies have been reported that block either CD40-dependent T-cell helper mediated B-cell proliferation or cytokine mediated B-cell proliferation [*see* Pound *et al.*, Intern'l Immunol. 11:11-20 (1999), included in Exhibit A]. All CD40 antibodies identified to date which block the binding of CD40 ligand to CD40 enhance proliferation.

Finally, the Applicant respectfully points out that the fact that CD40L exists as a trimer does not preclude the effectiveness of a monovalent agent to bind CD40 and stimulate B-cell proliferation. Indeed, Ledbetter *et al.*,[in *Crit. Review in Immun.* **17**:427-435 (1997), enclosed in Exhibit A] have shown that a monovalent single chain sFv from the variable region of the G28-5 monoclonal antibody for CD40 not only binds with a high affinity to CD40, but is also a potent agonist for B-cell proliferation.

In view of the above and foregoing, reconsideration and withdrawal of the objections and rejections under 35 U.S.C. § 112, first paragraph and second paragraph are respectfully solicited.

Rejection under 35 U.S.C. § 102 (a):

The Examiner has maintained his rejection for Claims 1-3, 5, 6, 8, 10, and 12 as being anticipated by Dullforce *et al.* The Examiner asserts that Dullforce *et al.* teach vaccinating with CD40 specific antibodies and polysaccharides. The Examiner has suggested that the Applicant supply a Katz-type Declaration to substantiate that this reference is the Applicant's own work.

In response to the Examiner's requirement, the Applicant submits a Declaration pursuant to 37 C.F.R. §1.132 in Exhibit B stating that the other co-authors of Dullforce *et al.* were not involved in the conception of the present invention. Therefore, Dullforce *et al.* is not a publication by "another" under 35 U.S.C. §102(a)

In view of the above and foregoing, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 (a) are respectfully solicited.

Rejection under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-10, 12, 13, and 15-23 as being obvious over Aruffo *et al.*, and/or Armitage *et al.*, and/or Ledbetter *et al.*, and/or Dullforce *et al.*, in view of Noelle, Mond *et al.*, Scott *et al.*, and Marburg *et al.* The Examiner asserts that Aruffo *et al.*, and/or Armitage *et al.*, and/or Ledbetter *et al.*, and/or Dullforce *et al.* use CD40 ligand or CD40-specific antibodies as adjuvants for vaccines to boost immune responses in various individuals. The Examiner admits that these references differ from the present Invention by not disclosing all of the methods and formulations of making the vaccines which comprise an adjuvant nor do they disclose the combination of an adjuvant with an antigen of interest. However, the Examiner asserts that the combination of an adjuvant with an antigen of interest was known in the art. Further, the Examiner asserts that vaccine formulations and methods of making the vaccines were all known at the time the invention was made. The Examiner further asserts that there were various means to make and formulate the vaccines for a number of antigens including both TD and TI antigens. The Examiner further asserts that the constructs comprising immunogenic compositions comprising an adjuvant and an antigen in which the adjuvant and antigen are joined together were also known.

Finally, the Examiner cites *In re Keller* 208 USPQ 871 (CCPA 1981) as holding that the test for combining teachings of the reference in an obviousness determination is what the combined teachings of the references would have suggested to those of ordinary skill in the art. The Examiner concludes that given the importance of signaling via the CD40 pathway, one of ordinary

skill in the art would have had an expectation of success in stimulating the immune response to a variety of antigens, as well as the motivation to provide CD40-specific adjuvants and antigens joined together as an efficient means to stimulate an effective immune response.

The Applicant respectfully traverses the Examiner's rejections. As indicated above Dullforce *et al.* is not prior art to the present invention. Furthermore, neither Aruffo *et al., nor* Armitage *et al.,* nor Ledbetter *et al.* teach the invention as claimed. Indeed, neither Aruffo *et al., nor* Armitage *et al.,* nor Ledbetter *et al.* disclose the linking or co-joining of the antigen to the adjuvant taught by the present invention. Therefore, the Examiner is forced to cure the deficiencies of Aruffo *et al.,* Armitage *et al.,* and Ledbetter *et al.* with additional teachings. In an attempt to provide such teachings, the Examiner cites Noelle, Mond *et al.*, Scott *et al.*, and Marburg *et al.* However, neither Noelle, nor Mond *et al.*, nor Scott *et al.*, nor Marburg *et al.* alone or in any combination can cure the deficiencies. Indeed, the Examiner essentially admits this and then relies on the ingenuity of the skilled artisan to formulate the present invention after careful review of all of the related art. Therefore, the Examiner uses hindsight to reconstruct a way for the skilled artisan to come to the present invention without the aid of the instant Disclosure. However, as explained by the U.S. Court of Appeals, Federal Circuit, such reconstruction, is impermissible:

> As this court has stated 'virtually all [inventions] are combinations of old elements." (citations omitted)... Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention... To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show motivation to combine the references that create the case of obviousness. *In re Rouffet* 47 USPQ2d 1453, 1457,1458 (Fed Cir 1998).

However, such motivation is uniquely contained by the Application as filed. Indeed, Chapter 7 of the book entitled "Vaccine Design, the Subunit and Adjuvant Approach" [*eds.*, M.F. Powell and M.J. Newman, New York pgs.141-228 (1995), enclosed in Exhibit A] details a

compendium of vaccine adjuvants and excipients, in an attempt to summarize all immunological adjuvants. In the vast majority of examples of adjuvants used, they are administered without linking or co-joining the antigen to the adjuvant. Therefore, linking or co-joining an adjuvant to with an antigen is not the standard practice of those having ordinary skill in the art. Consistently, a recent attempt by researchers from Stanford University to use CD40L as an adjuvant did not include the step of crosslinking the antigen to CD40L [Wong *et al.*, J. Immunology **162**:2251-2258 (1999), enclosed in Exhibit A]. Thus, the motivation for making the instant invention is only derived from the blueprint from the Applicant's own disclosure. Therefore the present invention is neither taught nor made obvious by Aruffo *et al.,* Armitage *et al.*, Ledbetter *et al.*, or Dullforce *et al.*, alone or in combination, or in further combination with Noelle, Mond *et al.*, Scott *et al.*, and/or Marburg *et al.*

In view of the above and foregoing, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103 are respectfully solicited.

In view of the foregoing amendments and remarks, reconsideration and early allowance of Claims 1-10, 12, 13, and 15-23 are respectfully requested. No additional fees are believed to be necessitated by the foregoing amendments. However, should this be erroneous, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages. Should the Examiner feel that a telephone conference would facilitate resolution of any of the above issues, he is invited to telephone the undersigned attorney.

In view of the above and foregoing, reconsideration and withdrawal of the outstanding grounds of rejection and early allowance of the claims as amended is believed to be in order and are respectfully solicited.

Respectfully submitted,

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PENDING CLAIMS

1. (Twice Amended) An immunogenic composition comprising an adjuvant and an antigen; wherein said adjuvant and said antigen are joined together; wherein said adjuvant is selected from the group consisting of an antibody that binds cell surface receptor CD40, a part of said antibody that is effective at binding CD40, and a CD40 ligand; and

wherein when said adjuvant binds to CD40 of a B-lymphocyte cell said adjuvant helps in activating said B-lymphocyte cell.

2. (Amended) A vaccine including the immunogenic composition according to Claim 1.

3. (Amended) A vaccine according to Claim 2 wherein said antigen is a T-cell dependent or T-cell independent antigen, or part of said T-cell dependent or T-cell independent antigen.

4. (Amended) A vaccine according to Claim 2 wherein said adjuvant is a CD40 ligand.

5. (Amended) A vaccine according to Claim 2 wherein said adjuvant is an antibody raised against said CD40, or a part of said antibody that is effective at binding CD40.

6. A vaccine according to Claim 5 wherein the antibody is monoclonal.

7. A vaccine according to Claim 5 wherein the antibody is humanised.

8. A vaccine according to Claim 3 wherein said antigen is soluble.

9. A vaccine according to Claim 3 wherein said antigen is a protein.

10. A vaccine A method wherein said antigen is a polysaccharide.

12. (Amended) A vaccine according to Claim 3 wherein said antigen is a protein or part thereof, and said antigen is fused to said adjuvant so as to provide a fusion protein.

13. (Amended) A vaccine according to Claim 2 further comprising at least one cytokine.

15. (Amended) A method for the manufacture of a vaccine capable of enhancing immunity comprising

(a) selecting a suitable T-cell dependent and/or T-cell independent antigen, or parts thereof, and

(b) associating or combining said antigen with an adjuvant; wherein said adjuvant is adapted to stimulate B-lymphocyte receptor, CD40.

16. A method according to Claim 15 wherein said vaccine is capable of enhancing T-cell independent immunity.

17. (Amended) A kit for the manufacture of a vaccine capable of enhancing T-cell independent or T-cell dependent immunity comprising a cell expressing a selected T-cell dependent and/or T-cell independent antigen, or parts thereof, and an adjuvant capable of stimulating a B-lymphocyte receptor, CD40.

18. (Amended) A kit according to Claim 17 wherein said vaccine is capable of enhancing T-cell independent immunity.

19. (Amended) A kit according to Claim 17 wherein one or both of said antigen and adjuvant is provided with a secretion signal whereby expression of one or both of said antigen or adjuvant results in secretion of one or both of said antigen or adjuvant from said cell.

20. (Amended) A kit according to Claim 17 wherein the expression of said antigen and adjuvant is adapted such that a single fusion protein can be manufactured by said cell.

21. (Amended) A kit according to Claim 20 wherein said single fusion protein is adapted for secretion from said cell.

22. (Amended) A nucleic acid molecule encoding the fusion protein according to Claim 12.

23. A nucleic acid molecule encoding a vaccine according to Claim 2.